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# Formulation and Evaluation of Captopril Loaded Niosomal Transdermal Films

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**Abstract:** Captopril was the first angiotensin-converting enzyme (ACE) inhibitor used for the management of hypertension. The aim of this study was to prepare and evaluate niosomal-loaded captopril transdermal films. Captopril has good solubility but has poor permeability and reduced bioavailability in the presence of food. The aim and objective are to improve bioavailability and permeability. The captopril-loaded niosomal formulations were prepared by thin film hydration technique, using materials like non-ionic surfactants such as Spans of different grades 20, 40, 60 and 80 and solvents like ethanol and chloroform. The FT-IR results revealed that there was no interaction between excipients and captopril. All the formulations showed better encapsulation efficiency. The dissolution studies showed prolonged drug release in comparison to pure captopril. On comprising all formulations, F3 showed sustained release of 98.44% up to 12hrs. The optimized niosomes of captopril were used to prepare transdermal films using methyl cellulose, HPMC E5, HPMC K4M and HPMC K15M as a film forming agents and dibutyl phthalate as a plasticizer. All the formulated captopril transdermal films were evaluated for drug content, folding endurance, weight variation and *in-vitro* drug permeation. The *in-vitro* drug permeation was found to be 99.58% over a period of 12 hrs. Based on the above results, administering niosomal-loaded captopril through the transdermal route is a better approach.

**Keywords:** Bioavailability, Captopril, Niosomes, Non-Ionic Surfactants, Permeability and Transdermal Films.

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## 1. INTRODUCTION

The treatment of a chronic disease or an acute disease has been generally accomplished by delivery of drugs to patients through various conventional dosage forms like capsules, tablets, liquids, aerosols and parenteral. This category of drug delivery is well-known to afford a prompt drug release. So, to achieve and maintain the concentration of a drug within the pharmacologically effective range, it is often required to take this type of conventional dosage form many times a day. This results in fluctuations in plasma drug concentration. Continuous I.V. infusion provides better systemic drug delivery that can maintain a constant and prolonged drug levels within a concentration range, which is therapeutically effective for treatment. But it requires continuous hospitalization during treatment and requires medical supervision. New techniques are developed that can control the drug delivery rate, prolong the duration of drug activity, and target the drug delivery to a particular site. The idea of delivering a drug through the skin laid efforts in the pharmaceutical field to develop a Transdermal drug delivery system to treat angina, hypertension, motion sickness and hormone deficiency.[1] Transdermal drug delivery system provides advantages. For instance, it is painless and easy to administer, it protects the active drug moiety from gastric substances and it, avoids first-pass metabolism, improved patient compliance, controls absorption rate, interference due to the presence of food is minimized, suitable for unconscious patients and enables termination of drug delivery if any side effects observed[2].According to a recent report, the value of the worldwide market for transdermal drug delivery was $12.7 billion in 2005 and $ 52.4 billion in 2020 and is expected to increase to $87.3 billion by 2030. Hypertension is a major situation that affects a large population of the world. Currently, a large number of oral medications are used for the treatment.[3]Transdermal drug delivery is the better alternative approach in the case when oral drug delivery is contraindicated, or poor absorption of the drug from G.I. tract.[4]Captopril was the first angiotensin-converting enzyme (ACE) inhibitor widely used for the management of congestive heart failure and hypertension. Captopril is considered a drug of choice in antihypertensive treatment due to its low toxicity and effectiveness. It has a $t_{1/2}$ of 2-3 hrs, but the action duration lasts 6-12 hrs. Captopril shows 75% bioavailability but reduces oral absorption to 30-50% in the presence of food, aiming to improve the bioavailability[5].The reduced bioavailability in the presence of food and short half-life makes captopril a good candidate for a transdermal drug delivery system (TDDS). A TDDS containing captopril avoids the reduction of bioavailability by drug intake or concomitant food and provides continuous dosing of the drug with improved patient compliance[6].The captopril oxidation rate in dermal homogenate is significantly lower than the intestinal homogenate because the captopril disulfide, an oxidative product of captopril shows poor absorption from the intestine[7]. When administered initially, captopril causes hypotension, which can harm congestive heart failure and diuretic-treated patients. Persistent hypotension may cause some trouble in myocardial infarction patients[8]. Therefore, using a transdermal drug delivery system of captopril can reduce the side effects. Niosome carriers, known for their potential in topical drug delivery, have been used to transport captopril molecules in the skin layer[9]. Niosomes of Captopril represents possible sustained-release formulation that increases the duration and magnitude of captopril[10]. The development of a once-daily captopril formulation would be a significant advantage for patient compliance, accompanied by minimizing drug side effects due to the reduction of drug blood concentration fluctuations in long-term therapy[11, 12]. It is well-known that transdermal applications greatly benefit from protecting drugs from the hepatic first-pass effect. However, the stratum corneum layer of the skin forms a barrier, resulting in slow absorption at the application site[13]. Captopril is generally marketed in the conventional dosage form of a tablet, usually with a strength of 12.5–50 mg. When the oral route administers the drug, it undergoes first-pass hepatic metabolism. The conventional tablet and capsule are administered 3 or 4 times a day due to their short biological half-life of about two hours. The bioavailability of captopril is reduced to 50% in the presence of food. The sustained release forms are administered two times a day due to their limited residence time in the gastrointestinal tract. These limitations of captopril in a conventional dosage form can be overcome by administering captopril through other routes of administration[14].The main objective of the present research work was to develop transdermal films of captopril that deliver the captopril at a controlled rate and evaluate the *in-vitro* characteristics of the captopril transdermal films. The research work's novelty is formulating the transdermal films using captopril-loaded niosomes instead of pure captopril, as Niosomal-loaded captopril showed enhanced drug release[15]. Niosomal-loaded captopril transdermal films were developed and examined due to their higher delivery rate, minimum film area, and low drug concentration.[16]

## 2. MATERIALS AND METHODS

### *2.1. Materials*

Captopril (A to Z Pharmaceuticals Ltd., Ambattur), MC, HPMC E5, HPMC K4M and HPMC K15M Di butyl phthalate (excel organic Pvt. Ltd., Chennai), Acetone (Merk Private Ltd., Mumbai), Ethanol (Changshu Hongsheng Fine Chemical Co. Ltd, China).

## 3. PREPARATION OF NIOSOMAL-LOADED CAPTOPRIL TRANSDERMAL FILMS

Niosomes, previously loaded with captopril by thin film hydration method, was used in the films' preparation. Transdermal films containing captopril were prepared using different concentrations of polymers (Methylcellulose, HPMC E5, HPMC K4M and HPMC K15M) individually or in combination. The drug concentration should be kept constant. The required amount of niosomal captopril (25 mg) and polymers were dispersed in solvents (Acetone and ethanol) and allowed to stir until the drug's and polymer's complete solubilization. After uniform mixing of the drug and polymer, the solution was allowed to stand for 10-20 minutes to remove air bubbles, and the final solution was poured into a petri dish. The polymeric drug solution allowed for evaporating for 24hrs to form a matrix film. After drying, the films were taken from the petri dish, cut to 2cm×2 cm, wrapped in butter paper and stored in desiccators for further studies.[17, 18] The compositions of different formulations are shown in Table 1 and 2.

**Table 1: Composition of captopril transdermal films**

| Quantities (mg) | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 | F10 |
|---|---|---|---|---|---|---|---|---|---|---|
| Captopril | 240.62 | 240.62 | 240.62 | 240.62 | 240.62 | 240.62 | 240.62 | 240.62 | 240.62 | 240.62 |
| Methylcellulose | 200 | - | - | - | 100 | 100 | 100 | - | - | - |
| HPMC E5 | - | 200 | - | - | 100 | - | - | 100 | 100 | - |
| HPMC K4M | - | - | 200 | - | - | 100 | - | 100 | - | 100 |
| HPMC K15M | - | - | - | 200 | - | - | 100 | - | 100 | 100 |
| Di butyl phthalate (ml) | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Acetone (ml) | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| Ethanol (ml) | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 |

***4 $cm^2$ contains 25 mg captopril***
***38.5 $cm^2$ contains 240.62 mg of captopril***
***240.62 mg captopril is equivalent to 1.20 g of niosomal-loaded captopril***

**Table 2: Composition of Niosomal Loaded Captopril Transdermal Films**

| Formulation code | Plasticizer % (Di butyl phthalate) | Polymer % | | | | Penetration enhancer % (Ethanol) |
|---|---|---|---|---|---|---|
| | | MC | HPMC E5 | HPMC K4M | HPMC K15M | |
| F1 | 5 | 100 | - | - | - | 10 |
| F2 | 5 | - | 100 | - | - | 10 |
| F3 | 5 | - | - | 100 | - | 10 |
| F4 | 5 | - | - | - | 100 | 10 |
| F5 | 5 | 50 | 50 | - | - | 10 |
| F6 | 5 | 50 | - | 50 | - | 10 |
| F7 | 5 | 50 | - | - | 50 | 10 |
| F8 | 5 | - | 50 | 50 | - | 10 |
| F9 | 5 | - | 50 | - | 50 | 10 |
| F10 | 5 | - | - | 50 | 50 | 10 |

## 4. EVALUATION OF NIOSOMAL LOADED CAPTOPRIL TRANSDERMAL FILMS

### *4.1. Compatibility study using FTIR and DSC*

Bruker company FT-IR was used to determine the pure drug's spectrums (Captopril) and its physical mixtures with polymers using the KBr pelletization method to find any possible reactions between the polymers and captopril. DSC Q20 V24.11 Build 124 was used to determine the potential chemical or physical interaction between polymers and captopril. [19, 20]

### *4.2. The physical appearance of the Formulation*

The prepared films were physically examined for colour, transparency and surface texture.[21]

### *4.3. Thickness*

The thickness of the captopril-loaded films was measured at different points using a digital micrometre and determine the average thickness to ensure the uniform thickness of the film.[22, 23]

### *4.4. Weight Uniformity*

Five different films from individual formulations were weighed using high-accuracy digital balance, and the average weight was calculated. The individual weight should not deviate extensively from the average weight.[24, 25]

### *4.5. Percentage of moisture loss*

The prepared films were weighed individually and stored in a desiccator containing calcium chloride at room temperature for 24hrs. After 24hrs, the films were reweighed, and the percentage moisture content was determined using the following equation.[26]

$$\% \text{ Moisture loss} = \frac{Initial\ weight - Final\ weight}{Final\ weight} \times 100$$

### *4.6. Percentage moisture uptake*

The weighed films were kept in desiccators at room temperature for 24hrs containing a saturated potassium chloride solution. After 24hrs, the films were reweighed, and the percentage moisture uptake was determined using the following formula.[27]

$$\% \ Moisture\ Uptake = \frac{Final\ weight - Initial\ weight}{Initial\ weight} \times 100$$

### 4.7. Folding endurance

The folding endurance was measured manually for the formulated films. A film of 2×2 cm was taken and folded at the same place until it breaks. The number of times the film would be folded at the same position without breaking gives the value of folding endurance.[28, 29,]

### 4.8. Surface pH

Transdermal films were left to swell for 1 hr on the surface of the agar plate prepared by dissolving 1% (w/v) agar in warmed phosphate buffer of pH 7.4 with continuous stirring and then poured the solution into the glass dish and allowed to stand till it forms a gel at room temperature. The surface pH was measured using a pH meter placed on the surface of the swelled film.[30]

### 4.9. Determination of tensile strength

The tensile strength is determined as the stretching force applied to the film at which it breaks. A specified weight was hung from the film through the sample such that a pulling force was produced. The force applied was measured in g/cm$^2$ on the load cell of the apparatus.[31]

### 4.10. Drug content

A film of 4 cm$^2$ was placed in a standard flask containing 10 ml of phosphate buffer of pH 7.4 and was sonicated for 20 mins using an ultrasonicator. The volume was made up to 100 ml, and the absorbance was measured at 212 nm by Spectrophotometer with suitable dilutions.[32, 33]

### 4.11. In-vitro permeation study

*An in-vitro* permeation study of prepared Captopril films was carried out using a Franz diffusion cell with 60ml capacity. Dialysis membrane (Hi-media) was used as a diffusion membrane. The diffusion cell was filled with phosphate buffer pH 7.4; the dialysis membrane was placed on the cell. The temperature was maintained at 37 ± 0.5°C. At regular time intervals, 5ml samples were withdrawn and replaced with phosphate buffer pH 7.4 after each sampling for 12hrs. The samples drawn were filtered and analyzed. The amount of permeated drug was determined using a U.V. Spectrophotometer at 212 nm. The experiments were done in triplicate. The amount of drug diffused was calculated for all formulations.[5, 34]

### 4.12. Stability Analysis

The optimized formulation transdermal films were stored at 40°C ± 2°C and 75% ±5% R.H. in stability chambers for three months. After three months, films were evaluated for weight variation, thickness and drug content.[35]

## 5. RESULTS AND DISCUSSION

Prepared films were found to be smooth, flexible and homogeneous[21]. The prepared formulations were evaluated for different physicochemical properties, as shown in Table 3. The weight of the films varied from 141.33 to 174.33 mg. The thickness of the films ranged from 222.67 to 274 µm[7]. The thickness of the films was uniform, indicating the uniform distribution of drug and polymer solution. The low standard deviation values represent uniformity in all formulations[36]. The percentage of Moisture loss of the prepared transdermal films was found to be between 2.31 to 6.12. The rate of Moisture uptake of the prepared transdermal films was found to be between 1.46 to 7.18. All the formulations showed lower moisture content. Lower moisture content in the formulations helps them to remain stable and become a wholly dried and brittle film. Low moisture uptake protects the formulated films from microbial contamination and bulkiness[37]. The variation in moisture uptake depends on the polymer's ability to absorb the moisture[38].

**Table 3: Different Physico-Chemical Properties of Captopril Films**

| Formulation code | Thickness (µm) | Weight Uniformity (mg) | % Moisture loss | % Moisture uptake |
|---|---|---|---|---|
| F1 | 254.67±2.52 | 163.00±1.00 | 3.01±0.79 | 2.75±0.79 |
| F2 | 222.67±1.53 | 141.33±2.52 | 5.98±1.33 | 7.18±1.51 |
| F3 | 234.00±1.00 | 146.67±2.08 | 6.12±1.07 | 5.56±2.40 |
| F4 | 243.67±3.06 | 152.33±1.15 | 4.23±1.90 | 3.84±2.07 |
| F5 | 236.33±0.58 | 148.00±1.00 | 5.36±3.18 | 3.67±1.48 |
| F6 | 244.67±1.53 | 153.33±1.53 | 5.60±2.76 | 3.13±2.05 |
| F7 | 274.00±2.65 | 174.33±3.06 | 2.31±1.27 | 1.46±0.64 |
| F8 | 228.33±1.15 | 146.67±2.08 | 4.38±0.02 | 5.26±1.31 |
| F9 | 240.67±1.53 | 149.33±1.53 | 3.59±2.48 | 4.98±1.49 |
| F10 | 261.00±2.00 | 168.67±1.53 | 3.19±1.55 | 2.43±0.59 |

*Values are mean ± S.D; (n= 3)*

Drug content was found to be in the range of 85.99 to 98.51%. The drug content of formulation F7 was higher than other formulations. This shows that the drug dispersed uniformly throughout the polymeric film[039,40]. The folding endurance test was performed manually, and maximum folding endurance was observed in formulation F7. If the films showed cracks on their surface, it was considered endpoint [1]. The results were satisfactory, indicating that the films would not break and would maintain their integrity when used [41]. The pH of all the formulations mimics the skin's pH of [42]. Tensile strength was in the range of 205 to 333.3. The results are shown in Table 4.

| Table 4: Evaluation Parameters of Captopril Films | | | | |
|---|---|---|---|---|
| Formulation code | % Drug content | Folding endurance | Surface pH | Tensile Strength (g/cm$^2$) |
| F1 | 95.63±0.10 | 97.3±2.5 | 5.40±0.17 | 235.3±3.2 |
| F2 | 85.99±0.16 | 84.0±3.6 | 5.33±0.15 | 205.0±3.6 |
| F3 | 89.80±0.18 | 92.7±1.5 | 5.43±0.06 | 222.3±4.0 |
| F4 | 94.14±0.22 | 107.3±2.1 | 5.53±0.21 | 259.3±2.5 |
| F5 | 87.89±0.24 | 87.7±1.5 | 5.60±0.26 | 210.3±4.0 |
| F6 | 94.17±0.31 | 110.7±2.1 | 5.83±0.25 | 265.7±4.7 |
| F7 | 98.51±0.52 | 138.0±3.6 | 5.80±0.46 | 333.3±4.5 |
| F8 | 89.46±0.53 | 87.3±1.5 | 5.70±0.53 | 209.7±4.0 |
| F9 | 88.35±0.55 | 90.7±2.1 | 5.77±0.42 | 218±4.6 |
| F10 | 95.32±0.52 | 99.3±2.5 | 5.50±0.79 | 237.7±4.2 |

***Values are mean ± S.D; (n= 3)***

### *5.1. Compatibility study using FT-IR and DSC*

Pure captopril showed principal absorption peaks at 672.35 cm$^{-1}$ (C-S stretch), 1193.64cm$^{-1}$ (C-N stretch), 1467.12 cm$^{-1}$ (C-H bend), 1581.90 cm$^{-1}$ (N-H bend) and 1740.90 cm$^{-1}$ (C=O stretch). The identical peaks of C-S stretching, C-N stretching, C-H bending, N-H bending, and C=O stretching vibrations were also noticed in the spectra of the drug mixed with polymers. FT-IR spectra revealed no interaction between the polymers and the drug used for transdermal film preparation[20,43]. The results are shown in Table No.5 and Figures 1-5. The DSC studies of captopril showed a peak at 110.41$^0$C. The DSC analysis of physical mixtures of captopril showed little change in the melting point of captopril. DSC studies revealed the absence of interactions between the drug and polymers[44]. The results are shown in Figure 6-10

| Table 5: FT-IR Interpretations of Pure Drug and Excipients | | | | | | | |
|---|---|---|---|---|---|---|---|
| S. No | Functional group | Characteristic peaks | Observed peaks | | | | |
| | | | Captopril (CAP) | CAP: MC | CAP: HPMC E5 | CAP: HPMC K4M | CAP: HPMC K15M |
| 1 | C-S (Stretching) | 600-800 cm$^{-1}$ | 672.35 cm$^{-1}$ | 670.09 cm$^{-1}$ | 671.07 cm$^{-1}$ | 668.40 cm$^{-1}$ | 669.76 cm$^{-1}$ |
| 2 | C-N (Stretching) | 1020-1250 cm$^{-1}$ | 1193.64 cm$^{-1}$ | 1220.93 cm$^{-1}$ | 1197.79 cm$^{-1}$ | 1220.85 cm$^{-1}$ | 1223.39 cm$^{-1}$ |
| 3 | C-H (Bending) | 1440-1480 cm$^{-1}$ | 1467.12 cm$^{-1}$ | 1476.40 cm$^{-1}$ | 1464.85 cm$^{-1}$ | 1463.76 cm$^{-1}$ | 1447.18 cm$^{-1}$ |
| 4 | N-H (Bending) | 1590-1650 cm$^{-1}$ | 1581.90 cm$^{-1}$ | 1581.63 cm$^{-1}$ | 1584.28 cm$^{-1}$ | 1581.78 cm$^{-1}$ | 1581.51 cm$^{-1}$ |
| 5 | C=O (Stretching) | 1690- 1760 cm$^{-1}$ | 1740.90 cm$^{-1}$ | 1743.24 cm$^{-1}$ | 1740.96 cm$^{-1}$ | 1741.47 cm$^{-1}$ | 1743.17 cm$^{-1}$ |

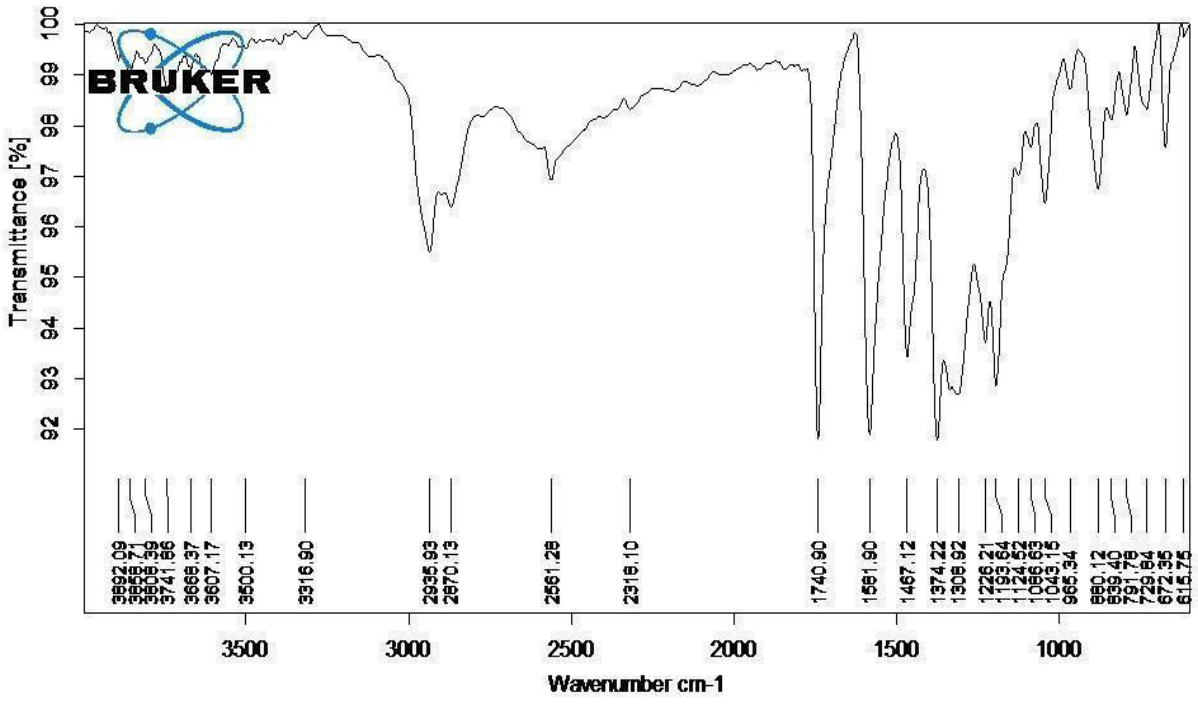


**Fig 1: FT-IR Spectrum of captopril**

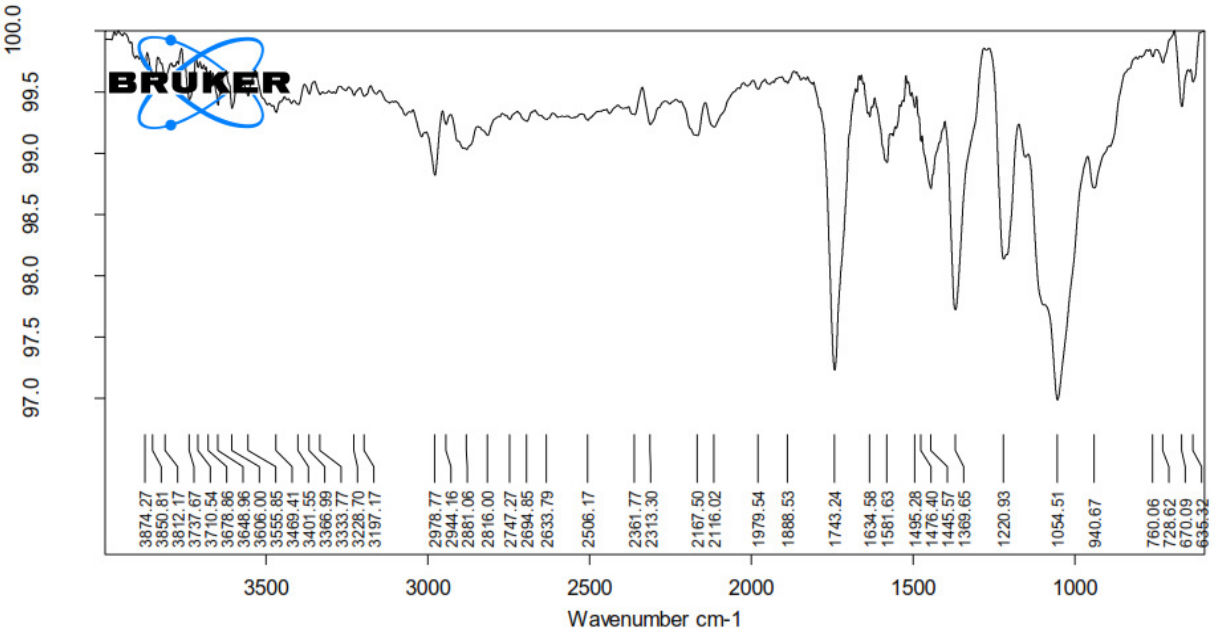


**Fig 2: FT-IR Spectrum of captopril with methylcellulose**

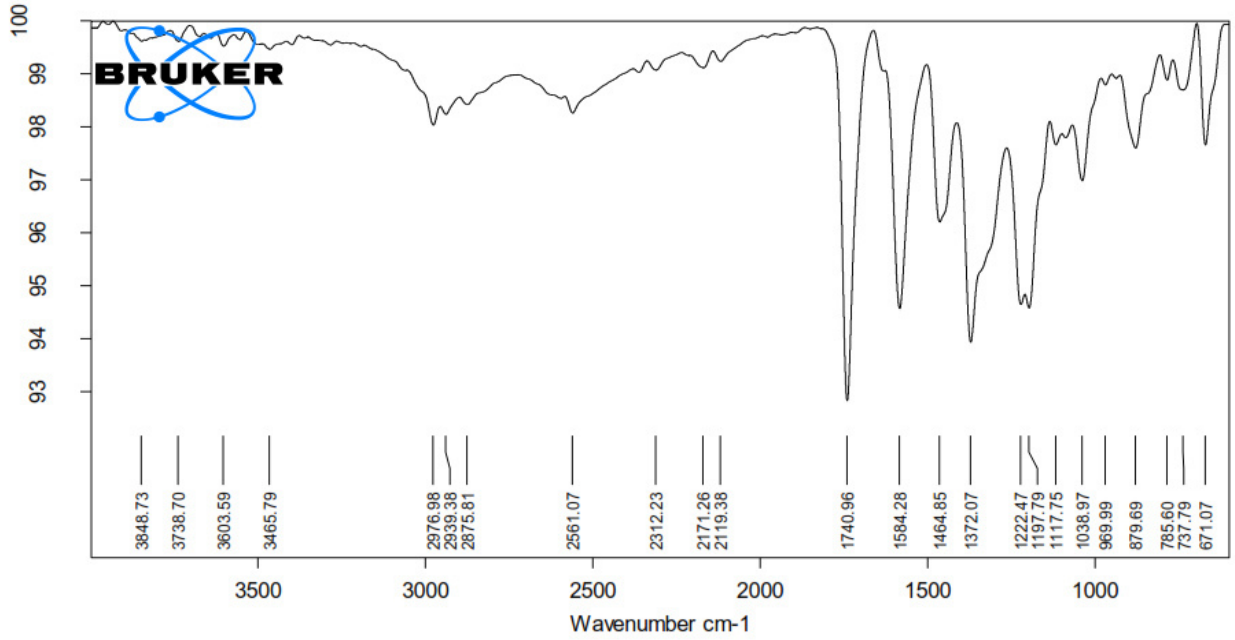


**Fig 3: FT-IR Spectrum of captopril with HPMC E5**

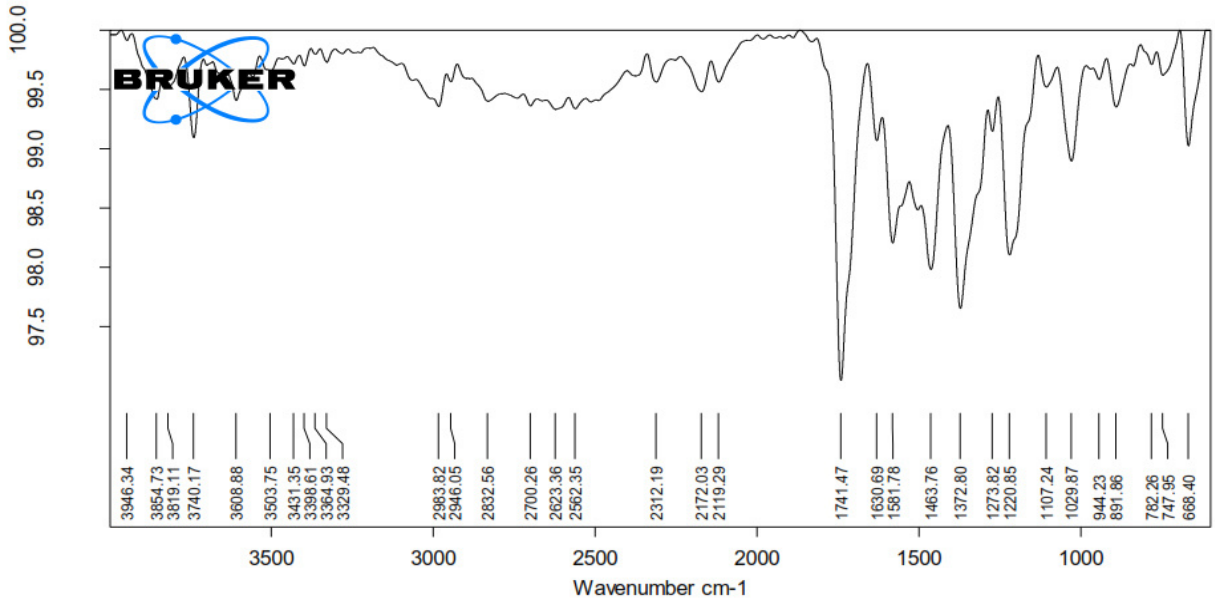


**Fig 4: FT-IR Spectrum of captopril with HPMC K4M**

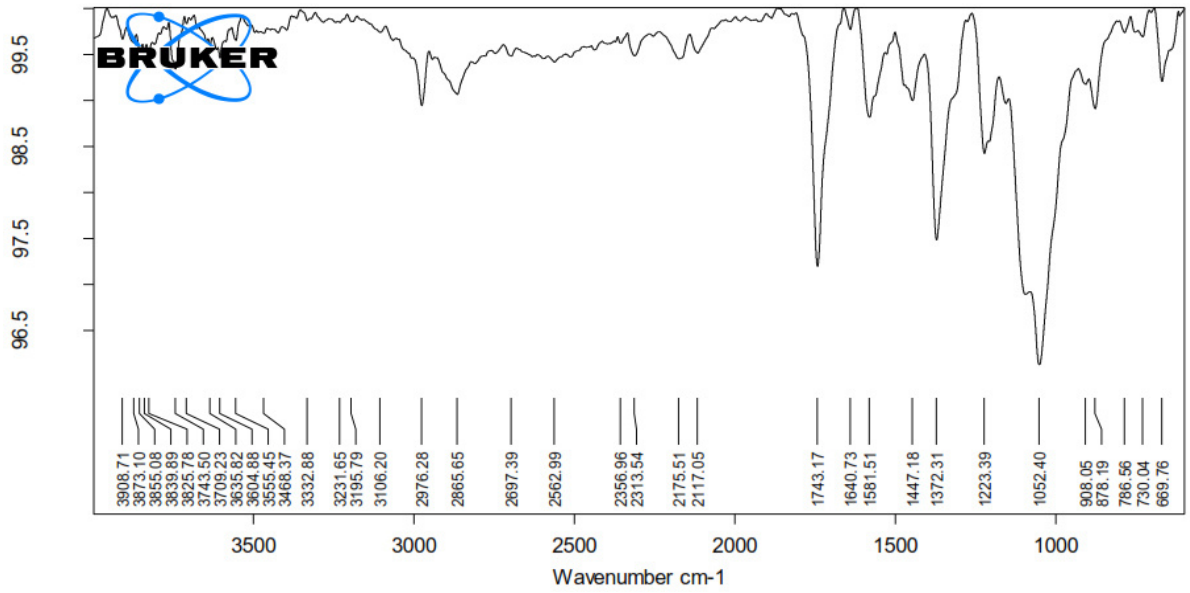


**Fig 5: FT-IR Spectrum of captopril with HPMC K15M**

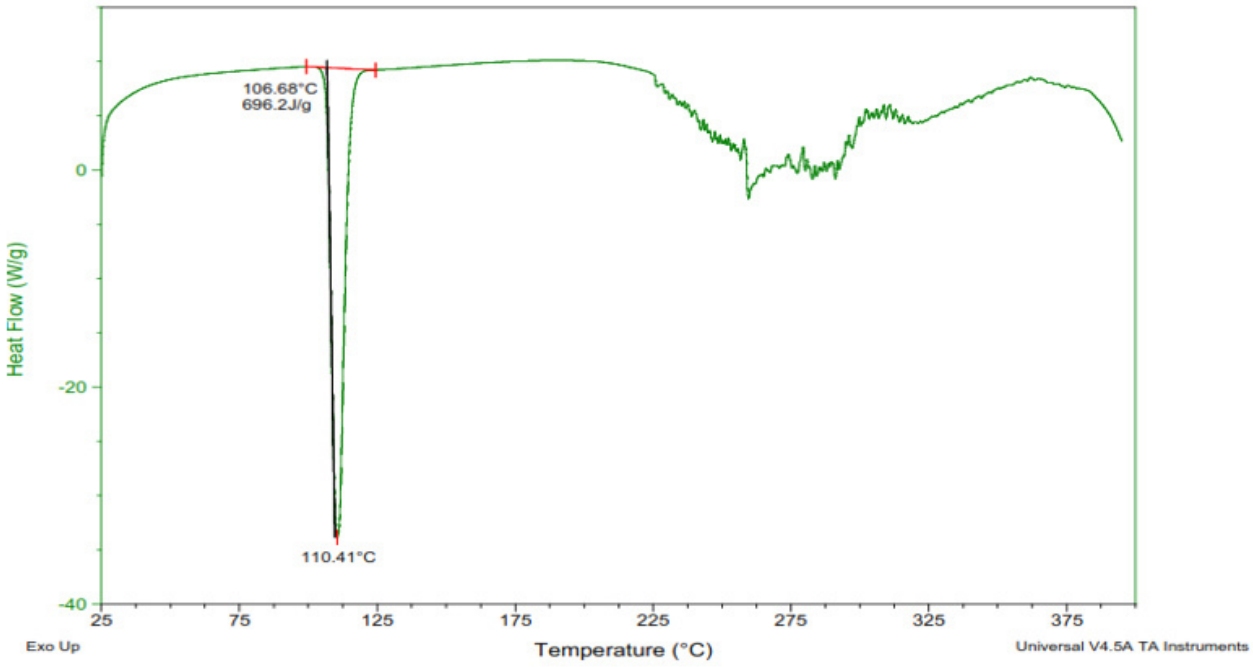


**Fig 6: DSC thermogram of captopril**

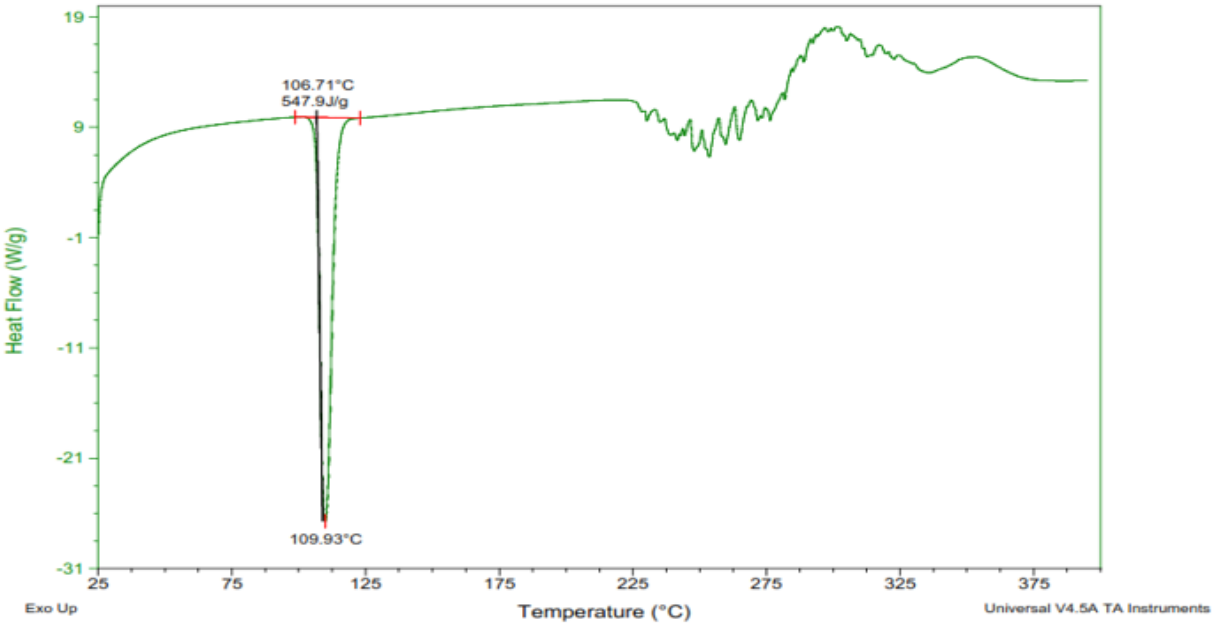


**Fig 7: DSC thermogram of captopril with methylcellulose**

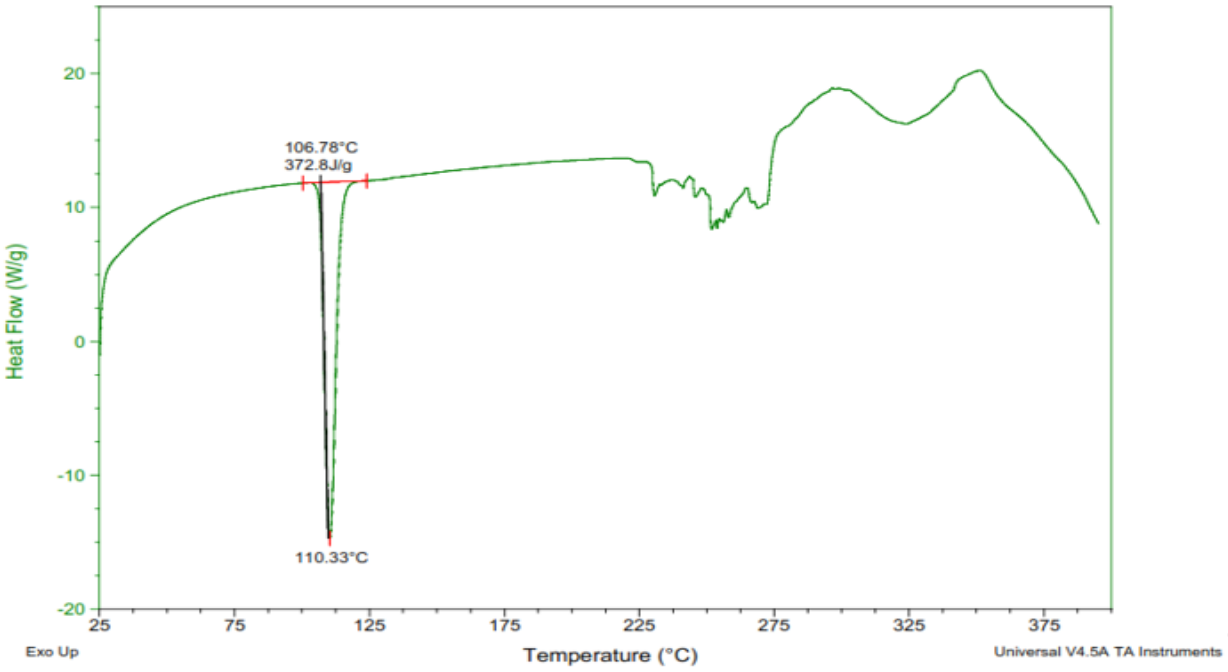


**Fig 8: DSC thermogram of captopril with HPMC E5**

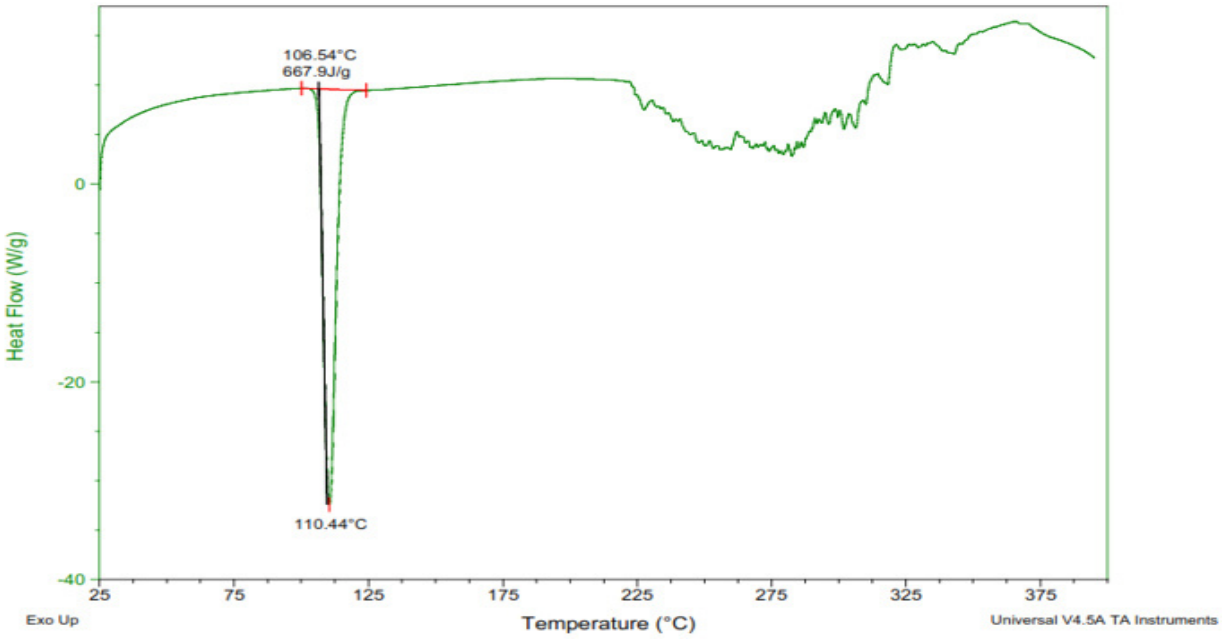


**Fig 9: DSC thermogram of captopril with HPMC K4M**

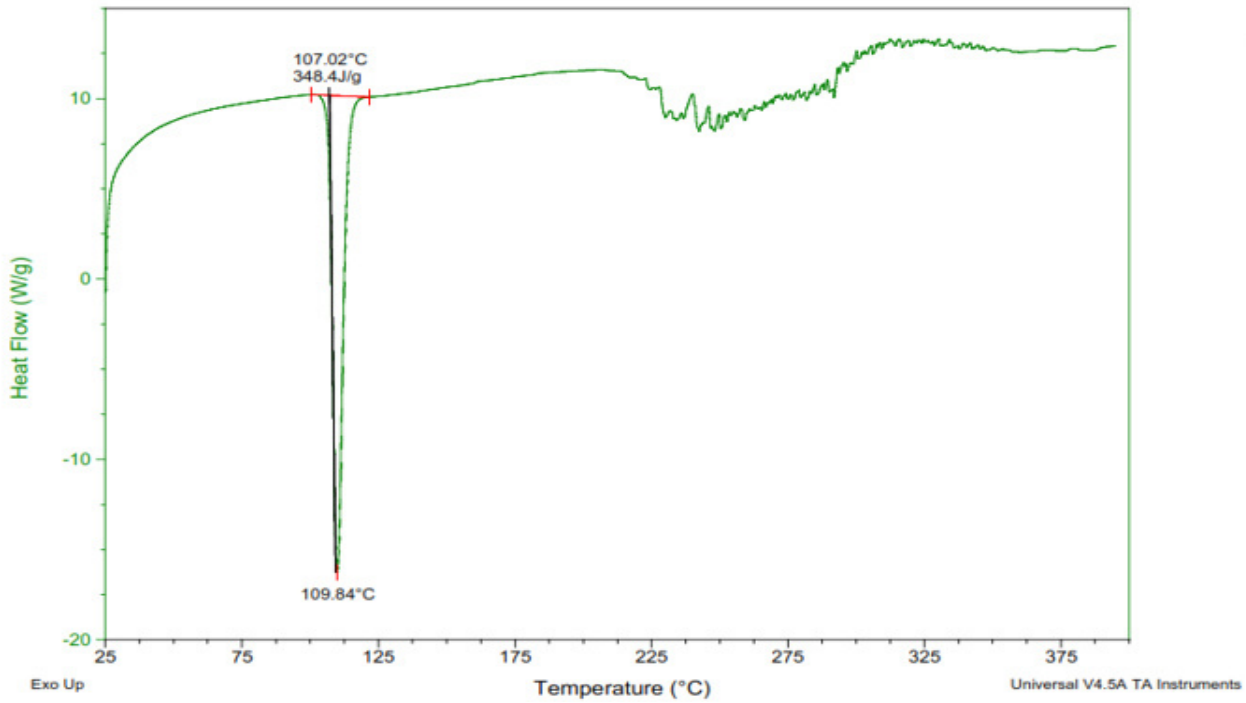


**Fig 10: DSC thermogram of captopril with HPMC K15M**

### 5.2. *In-vitro* permeation study

Captopril transdermal films were prepared by the Solvent casting method. All the formulations viz. F1-F10 cumulative permeation data are shown in Figure.11. *In-vitro* drug permeation studies were carried out using a Franz diffusion cell using a Hi-media dialysis membrane. The result of diffusion studies indicates that formulation F7 containing MC and HPMC K15M showed the highest drug permeation, 99.58 %, in 12 hrs. The high viscosity of MC and the swelling nature of HPMC may cause sustained release when compared to other formulations. The samples were analyzed spectrophotometrically at 212 nm[45].

### *5.3. Stability Analysis*

**Table 6: Stability Analysis of optimized Formulation (F7)**

| S. No | Observation | Initial | After 1 month | After 2 months | After 3 months |
|---|---|---|---|---|---|
| 1 | Average weight (g) | 174.33±3.06 | 173.00±2.00 | 172.33± 1.15 | 172.67± 3.51 |
| 2 | Thickness (µm) | 274.00±2.65 | 273.33±2.08 | 270.33±1.53 | 267.67±2.08 |
| 3 | Folding Endurance | 138.0±3.61 | 137.0±2.65 | 136.0±2.00 | 134.33±3.51 |
| 4 | Tensile Strength | 333.3±4.51 | 331.0±3.00 | 328.0±3.00 | 314.33±4.16 |
| 5 | Drug Content | 98.51±0.52 | 98.44±0.11 | 98.23±0.11 | 98.13±0.65 |
| 6 | Surface pH | 5.80±0.46 | 5.80±0.50 | 5.77±0.42 | 5.77±0.35 |
| 7 | Drug Permeation | 99.58±0.31 | 99.20±0.12 | 99.06±0.36 | 98.96±0.54 |

***Values are mean ± S.D; (n= 3)***

The results from stability analysis indicated that there was no significant difference. In addition, stability studies showed that optimized formulation F7 was stable. Therefore, all the stability studies were conducted as per ICH guidelines.

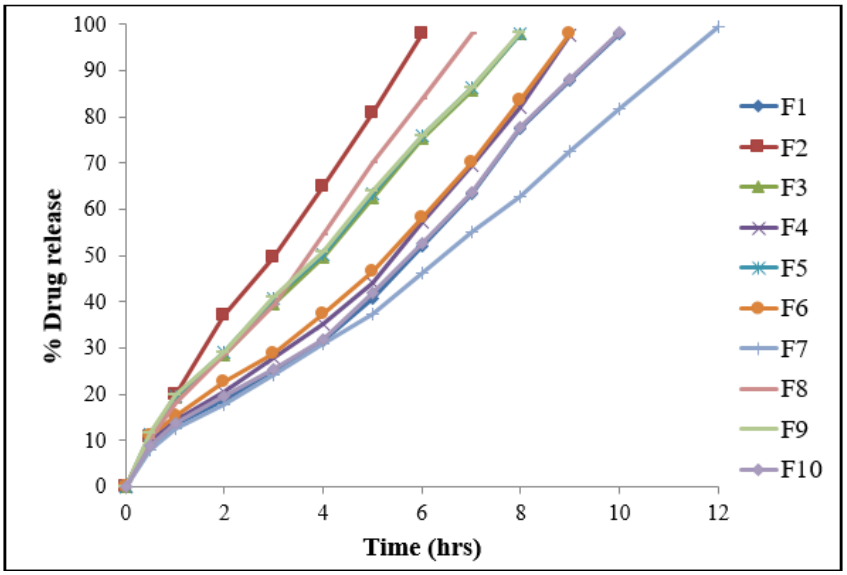


**Fig 11: *In-vitro* drug permeation profile of captopril transdermal films**

## 6. CONCLUSION

The optimized niosomal loaded captopril was taken for preparation of transdermal films by Solvent casting Method. MC, HPMC E5, HPMC K15M and HPMC K4M were used for the formulation of transdermal films. Dibutyl phthalate was used as a plasticizer, and ethanol was used as a permeation enhancer. Preformulation studies were performed to find drug-excipient interactions. FT-IR spectra revealed no interaction between the drug and the polymers used to prepare transdermal films. The prepared Captopril transdermal films were evaluated for thickness, weight uniformity, % Moisture loss, % Moisture uptake, Folding endurance, Tensile strength, Surface pH and % Drug content. *In addition, in-vitro* permeation studies were performed. Good results were obtained for evaluated parameters and *in vitro* studies. F7 formulation containing HPMC K4M and HPMC K15M exhibited the release of 99.58% up to 12 hrs. The results from stability analysis indicated that there was no significant difference and found to be stable.

## 7. AUTHORS CONTRIBUTION STATEMENT

Mr Angilicam Avinash gathered the materials required and designed the formulation methodology for this research work. Dr P. Dwarakanadha Reddy and Prof. S. V. Satyanarayana performed formulations trials for designing the final methods. All authors discussed the results obtained and contributed to writing the manuscript.

## 8. CONFLICT OF INTEREST

Conflict of interest declared none.

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